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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,265	11/12/2003	Sam Hwang	224738	5821

45733 7590 05/17/2005

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EXAMINER	
HARLE, JENNIFER I	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/706,265	HWANG, SAM	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *12-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 36-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-39 are pending and were the subject of an Election/Restriction Requirement.

2. Claims 1-11 and 36-39 are pending, claims 12-35 are withdrawn in light of Applicant's Response to the Election/Restriction Requirement.

Election/Restrictions

3. Applicant's election with traverse of Group I, claims 1-11 and 36-39, species SEQ ID NO 2 in the reply filed on February 28, 2005 is acknowledged. The traversal is on the following ground(s):

a. That claim 11, unlike the other claims of group I is directed to a method involving the use of an antagonist of CXCR4 and thus does not appear that it should be included in Group I.

b. That there is no serious burden in searching each of the individual groups

c. That the species election is improper for two reasons 1) because the restriction fails to allege that any of the species are patentably distinct claimed by the embraced genus or 2) each of the genus(s) claimed is directed to an unreasonable number of species, i.e. the restriction does not identify more than one species in group I.

This is not found persuasive because:

a. Claim 11 can be a linking claim encompassing the subject matter of claim 1, T22 for example is a known antagonist of CXCR4 and is also not an antibody that binds to CXCR4 (See Murakami, et al., A Small Molecule CXCR4 Inhibitor that Blocks T Cell Line-tropic HIV-1 Infection, Journal of Experimental Medicine, 1997, Vol. 186, No. 8, pp. 1389-1393, esp. Summary, pg. 1389 and 1391)

b. There would be a serious search burden on the examiner to search each Group. The formula of Group I alone comprises thousands of different peptide permutations that can be linear, cyclic or dicyclic. Group II comprises any antagonist of beta one integrin and includes antibodies, peptides or peptidomimetics (including receptor binding portions for a ligand, i.e. can have the amino acid sequence RGD), ligands (i.e. fibronectin, laminin, VCAM-1), etc. See Applicant's own Specification, pg. 5, [0020]. These compounds cross divergent areas, i.e. antibodies, peptides and peptidomimetics to name a few and encompass a plethora of compounds. Group III comprises any antagonist of CXCL12 and again includes antibodies, peptides or peptidomimetics, which cross divergent areas and encompass a plethora of compounds (the plethora of possibilities are set forth for example on pp. 5-6 of Applicant's Specification). Group IV comprises any antagonist of alpha four integrin CXCL12 and again includes antibodies, peptides or peptidomimetics, which cross divergent areas and encompass a plethora of compounds (the plethora of possibilities are set forth for example on pg. 6 of Applicant's Specification). First, as previously set forth by the examiner, these inventions are unrelated. The instant specification did not disclose that these methods would be used together. The method of inhibiting metastasis of a tumor cell in a mammal using a polypeptide of the specific formula/an antagonist of CSCR4 that is not an antibody that binds to CXCR4 (group I), the method of inhibiting metastasis of a tumor cell in a mammal using an antagonist of beta one integrin (group II), the method of inhibiting metastasis of a tumor cell in a mammal using an antagonist of CXCL12 (group III), and the method of inhibiting metastasis of a tumor cell in a mammal using an antagonist of alpha four integrin (group IV) are all unrelated as they comprise different products which demonstrates that each has a different mode of operation, as previously

set forth. Each invention performs this function using a structurally and functionally divergent material. Furthermore, although argued that it would not be burdensome, the search clearly would be burdensome. Searching each group together would impose a serious search burden. Each different group of compounds must be separately searched and each group contains a plethora of its own compounds then the search must be related to the method of inhibiting metastasis. The search for the compounds group I is not going to be co-extensive with any of the other groups and vice versa. The additional searching with the method would also not be co-extensive and the synonyms would not overlap with the compounds nor would the broad concepts of each group. Thus, it would be burdensome to search the groups together.

c. The species election is proper for the same reasons that the Group elections are proper. Searching each group in its entirety is burdensome. Applicant's argument that the examiner did not specifically identify the plethora of compounds from which they were able to make their election is not persuasive. The examiner is not required to specify every possible compound. The MPEP in section 809.02 merely requires that the examiner identify exemplary ones, which he did, i.e. SEQ ID NO 2 and specific peptides of the formula of SEQ ID NO1 (convenient characteristics) for Group 1 and specific antagonists (convenient characteristics) for the other groups. The examiner also grouped the generic claims and set forth reasons for patentable distinct ness, i.e. their structure. As previously set forth each set of species contains a plethora of compounds, see above and pp. 4-6 of the specification rendering the search of search species unduly burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Claims 12-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions II-IV, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 28, 2004.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6, 11, 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Koshiba, et al., Expression of Stromal Cell-derived Factor 1 and CXCR4 Ligand Receptor System in Pancreatic Cancer: A Possible Role for Tumor Progression, Clinical Cancer Research, September 2000, Vol. 6, pp. 3530-3535.

Koshiba disclosed that SDF-1 is a member of the CXC subfamily of chemokines, and its chemotactic effect is mediated by the chemokine receptor CXCR4 but unlike other chemokines, the SDF-1/CSCR4 receptor ligand system has been shown to involve a one-on-one interaction. Koshiba also disclosed that in order to clarify the role of the SDF-1/CSCR4 receptor ligand system in pancreatic cancer, they investigated the expression of CXCR4 and SDF-1 with the aid of immuno histochemical analysis and RT-PCR in pancreatic cancer tissue and experimental chemotactic activity of SDF-1 in pancreatic cancer cells and vascular endothelial cells *in vitro*. Pg. 3530. Koshiba further disclosed that CXCR4 immunoreactivities were observed in endothelial cells of relatively large vessels around tumorous lesions but were scarcely found in

the endothelial cells or microvessels inside tuorous lesions and that one micromolar of T22 caused a 33% reduction of the chemotaxis of endothelial cells (HUVECs) in the presence of 100 ng/ml SDF-1. and T22 significantly reduced the chemo attractive effect in the migration assay for pancreatic cancer cells (CFPAC-1). Pg. 3533. Thus, Koshiba concluded that the results indicate that the paracrine mechanisms may be involved in the SDF-1/VCSCR4 receptor ligand system in pancreatic caner and that they have demonstrated that CXCR4 mRNS expression was present in HUVEC endothelial cells and that the migratory capability of HUVECs was increased by SDF-1 stimulation further suggesting that SDF-1/CXCR4 receptor ligand system may be involved in angiogenesis. Pg. 3534. Koshiba supports this conclusion by disclosing that it was recently demonstrated that SDF-1 plays an important role in organ vascularization and the death of CXCR4 knockout mice – noting the lack of direct evidence of CXCR4 expression in microvessels inside the tumor, Koshiba states that SDF-1 may be involved in tumor growth by way of modeling relative large vessels in pancreatic cancer cells. Pg. 3534. Thus, Koshiba concludes that T22 is a small synthesized peptide that is a CXCR4 antagonist that inhibits CA2+ mobilization induced by SDF-1 stimulation through CXCR4, i.e. T22 significantly antagonized SDF-1 stimulated migration of AsPC-1 pancreatic cancer cells and HUVEC endothelial cells (metastisis of organ cells expressing SDF-1). Pg. 3534. Koshiba additionally concludes that it is well known that the interaction between cancer cells and stromal cells is deeply involved in tumor invasion and metastasis and that they were able to demonstrate that MRC-9 fibroblast cells significantly increased the migratory capability of CFPAC-1 cells and that T22 significantly decreased this capability. Pg. 3534. Koshiba further concludes that the *in vitro* findings indicate that SDF-1 acts as a chemoattractive factor for pancreatic cancer cells and endothelial cells and

is, at least in part involved in the mechanism of cancer cell migration resulting from fibroblast coculture, while noting that in this situation *in vitro* migration assays may not predict *in vivo* function, thus the results suggest that SDF-1/CXCR4 receptor ligand system may have a possible role in the pancreatic cancer progression through tumor cell migration and angiogenesis. Pg. 3535. Koshiba moreover states that because T22 suppressed the migration of both pancreatic cancer cells and endothelial cells *in vitro*, additional *in vivo* studies are warranted to examine whether T22 suppresses the tumor spread (inhibits metastasis) and tumor angiogenesis[1] (tumor growth) to clarify the role of the SDF-1/CXCR4 receptor ligand system in pancreatic cancer. Pg. 3535. Thus, one of ordinary skill in the art at the time of the invention would have been motivated to have inhibited metastasis of a pancreatic tumor cell - in a mammal and inhibiting growth of a pancreatic tumor cell in a mammal where the tumor cell expresses CXCR4 and the growth is stimulated by SDF-1, i.e. a mouse, utilizing polypeptide T22 because of the express suggestion in Koshiba to clarify the role of the SDF-1/CXCR4 receptor ligand system in pancreatic cancer *in vivo* given the fact that the *in vitro* data already supported inhibiting metastasis of a tumor cell, where in the tumor cell expresses CXCR4 and the pancreas cells express SDF-1 and to inhibit tumor cell growth where the tumor cell expresses CXCR4 and the growth is stimulated by SDF-1.

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[1] Antiangiogenesis; refers to the impact of any compound that works to prevent angiogenesis (i.e., formation/development of new blood vessels). Because angiogenesis is required for malignant turos to grow and/or metastasize (spread), antiangiogenesis was proposed as a means to combat cancer, by Judah Folkman in 1970. For example, the biotechnology-derived pharmaceutical known as Avastatin® (hbevacizumab) has been proven to be effective against metastic colorectal cancer, some lung cancers and some breast cancers. It acts by 'starving' cancerous tumors of the blood supply (i.e., new blood vessels/feeders) those tumors need in order to survive and grow. Because angiogenesis is required for embryonic development, anti-angiogenic drugs inhibit proper development/growth of infants in the womb. Drugs that have been found to possess antiangiogenic properties include Avastin®, fumagillin, ovalicin, and Thalidomide. Also the human proteins angiostatin and endostatin. See Antangiogenesis, Biotechterms.org, 2001, pg, 1, http://biotechterms.org/sourcebook/savelinktermquery.php3?ANTIANGIOGENESIS, printed May 13, 2005.

5. Claims 1-7, 11 and 36-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koshiba, et al., Expression of Stromal Cell-derived Factor 1 and CXCR4 Ligand Receptor System in Pancreatic Cancer: A Possible Role for Tumor Progression, Clinical Cancer Research, September 2000, Vol. 6, pp. 3530-3535 in view of Murphy, et al. (WO 99/50461).

Koshiba discloses as set forth above. However, Koshiba does not disclose that the organs are the skin, liver, brain and/or lung or that the tuor cell is a breast cancer cell, a breast tumor cell, a lymphoma cell, a neuroblastoma cell a lung caner cell, an angiosarcoma cell, a leukemia cell, a prostate cancer cell or a melanoma cell. Murphy discloses that CXCR-4 is involved in cell transformation and aberrant cellular proliferation and that modulation of CXCR-4 activity and/or by interference with its ligand SDF-1 can result in pharmaceuticals that are antagonists to CXCR-4. Pp. 4-8 and 19-20. Murphy further discloses that CXCR-4 in the presence of its ligand SDFβ-1, is required for the proliferation of tumor cells and the inhibition of CXCR-4 gene expression or the inhibition of CXCR-4 activity in transformed cells reverses the transformed phenotype, i.e. inhibit EXCR-4 expression or inhibit the interaction between CXCR-4 and its ligand, e.g. SDF-1 and that such identified agents have utility in the treatment of hosts demonstrating a cellular transformed phenotype or aberrant cellular proliferative behavior (tumor growth), and advantageously would be effective to treat and/or prevent tumorigenesis (metastasis). PP. 14 and 16. Murphy additionally discloses that CXCR-4 is over-expressed in several brain tumor derived cell lines and primary brain tumor tissues, including neuroblastoma, and nueuroectodermal human tumor cell lines, medulloblastoma and astrocytoma grade III cell lines, and primary glioma, and meningioma tumors, as well as being overexpressed in breast tumor tissues, lymphoblstic leukemia cell lines, Burkitt's lymphoa cell lines, colorectal

adrenocarcinoma, lung carcinoma, and melanoma cell lines. Pp. 17-18. Murphy discloses disorders involving tumorigenesis or cell over proliferation are treated or prevented by administration of a therapeutic that antagonizes (i.e. inhibits) CXCR-4 function, as demonstrated using in vitro assay and animal models, and include Leukemia, Lymphoma, Multiple myeloma, hepatoma (liver cells/liver), melanoma (skin cells/skin), angiosarcoma, lung carcinoma, squamous cell carcinoma , glioblastoma, basal cell carcinoma (For a complete listing Table 1, pp. 52-54). Pp. 52-54. Murphy further discloses that any of the malignancies or disorders in Table 1 can be treated in pre-malignant conditions to prevent progression to a neoplastic or malignant state, in particular where non-neoplastic cell growth consisting of hyperplasia (controlled cell proliferation involved an increase in cell number in a tissue or organ, without significant alteration in structure or function), metaplasia, or most particularly dysplasia has occurred. Pp. 54-56. Murphy additionally discloses the ability to provide animal models for diseases and disorder involved cell hyperproliferation or malignancy and the use of in vitro models. Pp. 88-89; Various portion of the specification, e.g. 89-105 Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to have utilized the T22 and its method to inhibit metastasis of other types of tumor cells, including where the organ is the skin, liver, brain or lung and where the tumor cell is a breast cancer cell, a breast tumor cell, a lymphoma cell, a neuroblastoma cell, a lung cancer cell an angiosarcoma cell a leukemia cell a prostate cell or a melanoma cell because Murphy explicitly teaches the use of a Therapeutic[2] to prevent and treat tumorgenesis (the production of tumors, i.e. metastasis and tumor growth) and cell proliferation (tumor growth) as well as prevent and treat these metastasis of these types and

[2] Murphy defines therapeutics to include but not be limited to CXCR-4 antagonists. See pg. 50.

that CXCr-4 in the presence of its ligand SDF-1 is required for the proliferation of tumor cells, the same as Koshiba and pancreatic cancer, i.e. the same mechanism is involved in the disease state and the same mechanism is involved the therapeutic.

6. Claims 1-11 and 36-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koshiba, et al., Expression of Stromal Cell-derived Factor 1 and CXCR4 Ligand Receptor System in Pancreatic Cancer: A Possible Role for Tumor Progression, Clinical Cancer Research, September 2000, Vol. 6, pp. 3530-3535 in view of Murphy, et al. (WO 99/50461) and further in view of Clark-Lewis (WO 99/47158).

Koshiba and Murphy disclose as set forth above. Clark-Lewis discloses a variety of therapeutic uses for CXCR4 antagonists, including cancer. Abstract. Clark-Lewis further discloses that the pharmaceutical compositions containing CXCR4 antagonists be administered in a therapeutically effective amount and dosing regimen, which is described as being varying according an amount effect, at dosages and for periods of time necessary to achieve the desired therapeutic result, such as reduction or reversal of angiogenesis in the case of cancers – noting that the therapeutically effective amount of CXCR4 antagonist may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the CXCR4 antagonist to elicit a desired response from the individual, dosage regimens may be adjusted to provide the optimum therapeutic response, dosing regimens should be adjusted over time and can be administered intraperitoneally. Pp. 14-17.Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to have administered the polypeptide intraperitoneally to the mammal on a daily basis for at least two days, as this is merely a dosing regimen that is routine optimization, as taught by Clark-Lewis.

Conclusion

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Matsumoto, et al. (US 5,776,899), discloses that T22 is the best mode for treating HIV.

Murakimi, et al., A Small Molecule CXCR4 Inhibitor that Blocks T Cell Line-tropic HIV-1 Infection, J. Exp. Med., 1997, Vol. 186, No. 8, pp. 1389-1393 discloses that T22 is a CXCR4 small molecule inhibitor.

Giminder, et al., A Possible Role for CXCR4 and Its Ligand, the CXC Chemokine Stromal Cell-Derive Factor –1, in the Development of Bone Marrow Metastases in Neuroblastoma, Journal of Immunology, October 15, 2001, Vol. 167, pp. 4747-4757, discloses that the ability of neuroblastoma tumors to form metastases in the bone marrow may be influenced by a set of complet CXCR4-SDF-1 interactions.

Malcom A.S. Moore, The role of chemoattraction in cancer metastases, BioEssays, July 25, 2001, Vol. 23, 674-676, discloses that hematopoietic stem cells express the chemokine recptor CXCR4 , and its ligand stromal derived factor-1 (SDF-1) is express within the marro environment (oseoblasts, stromal cells, endothelial cells) and thatCSCR# was highly expressed in malignant but not normal breast cancer tissue and its ligand, SDF-1 (CXCL12), was expressed in those organs were breast cancer metastases are frequently found (bone, marrow, lymp nofdr, lung).

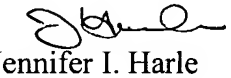
Muller, et al., Involvement of chemokine receptors in breast cancer metastasis, discloses that in vivo neutralizing the interactions of CXCL12(SDF-1)/CSCR4 leads to a significant inhibition of lymph-node and lung metastasis and that currently intense efforts are underway to

identify small-molecule antagonists for many chemokine receptors, including small molecule antagonists of chemokine receptos suchs as CXCR4, may be useful to interfere with tumor progression and metastasis in tumor patients.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Jennifer I. Harle
Examiner
Art Unit 1654

May 13, 2005